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(54) Title: ANTIVIRAL PHARMACEUTICAL COMPOSITIONS FOR VAGINAL ADMINISTRATION

(57) Abstract

Biocompatible sustained-release vaginal antiviral compositions in form of effervescent tablets, bioadhesive tablets, bi-layered tablets, bioadhesive washes, are described.

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ANTIVIRAL PHARMACEUTICAL COMPOSITIONS FOR VAGINAL ADMINISTRATION

The present invention refers to antiviral pharmaceutical compositions for vaginal administration.

Particular attention has been recently paid to the administration of drugs by the vaginal route in order to obtain, beside local effects, also systemic effects.

Usually, the drug is carried in form of vaginal ovules comprising semisynthetic glycerides (Remington's Pharmaceutical Sciences 17 Ex. p. 582) or natural fats (e.g. cocoa butter) having normally a melting or softening point at about 37°C, allowing the release of the drug for the absorption.

The drug may be solubilized in the fatty components or it may be homogeneously dispersed therein.

Other known forms for vaginal use include soft capsules, suited for non-hydrophilic, liquid drugs, oily dispersions or solutions, vaginal washes, ointments, gels.

The known compositions are not satisfactory since they cannot provide a sufficiently long permanence of the drug in contact with the vaginal mucosa.

Antiviral drugs are particularly suited for the vaginal administration.

The present invention provides prompt and/or sustained release antiviral compositions for vaginal administrations.

The sustained or prolonged r lease after vaginal administration may be obtained according to the

invention by means of effervescent compositions; slowly erodible and/or disgregating hydrophilic tablets; bioadhesive, hydrophilic tablets; bi-layered tablets wherein a first layer is able to release immediately the drug and the second layer provides the sustained release of the drug by means of bioadhesive biocompatible polymers; washes, gels or ointments containing biocompatible bioadhesive polymers.

Example of antiviral drugs which may be used according to the invention include: acycloguanosine (acyclovir) or its salts or derivatives, trifluridine, bromovinyldeoxyuridine, desciclovir, enviroxime, foscarnet sodium, ganciclovir, idoxuridine, inosine pranobex, interferons (α, β, γ), rimantadine hydrochloride, ribavirine, vidarabine and derivatives, zidovudine or azidothymidine.

Acycloguanosine or acyclovir (The Extra Pharmacopoeia 29th Ed., p. 689) is particularly preferred.

According to a first preferred embodiment, the invention provides therefore antiviral vaginal tablets formulated so as to cause, when in contact with the liquids present in the application site, a slight, progressive and slow effervescence. The selection of the appropriate amounts of a organic and biocompatible acid and of an alkaline carbonate or bicarbonate will provide the desired effect.

A second preferred embodiment is provided by vaginal tablets releasing the drug in a period from some hours to some days, thanks to suitable hydrophilic polymers. Examples of said hydrophilic polymers

include: xantanes, galactomannanes, carboxyvinyl-polymers, cellulose derivatives such as methylcellulose, ethylcellulose, sodium carboxymethyl-cellulose, hydroxypropylcellulose, hydroxypropylmethyl-cellulose.

Preferably hydroxypropylmethylcelluloses characterized by different average molecular weights and viscosities (generally measured on 2 w% aqueous solutions with a suitable viscosimeter), can be used.

Also hydroxypropylmethylcelluloses with the same average molecular weight, but with different degree of substitution or different methoxyl/hydroxypropoxyl substituent ratio can be used, having therefore different gellable and/or erodible characteristics. As a consequence the dosage forms formulated with these polymers can show different solubilization rates and different retention times in the administration site.

Hydroxypropylmethylcelluloses commercial products are characterized by different methoxyl/hydroxypropoxyl substituent ratios (namely the substituents of the anhydroglucose units of cellulose) that influences aqueous/organic solubility and terminal gel point temperature of aqueous solutions. As an example the hydroxypropylmethylcellulose marketed with the trade mark of Methocel® type E, type F and type K, is characterized by different propylene glycol ether to methoxyl substitution ratios on the same polymer backbone, and, moreover, each type is produced in wide range of average molecular weights.

Said polymers can be employed in the formulation in a percentage ranging from 5 to 95% (depending on

drug solubility and as a function of the programmed drug release rate from the dosage form), but preferably this polymers are used in amounts varying from 15 to 60 w/w%.

A further preferred embodiment is provided by pharmaceutical forms devised for a pulsing release of the drug, i.e. able to release immediately a first portion of the drug and a second portion in a prolonged period of time. It is therefore possible a simpler posology and a better patient compliance. This kind of formulation may consist in bi-layered tablets as defined above. Still a further preferred embodiment is provided by vaginal tablets comprising bioadhesive polymers such as gelatine, xantanes, scleroglucane, collagene, pectine and amylopectine, dextranes, hyaluronic or polygalactouronic acid, alginic acid, alginates, polyvinylpyrrolidone, polyvinylalcohol, polyethylenglycols, polypropylenglycols and copolymers, polymethylvinylether maleic anhydride copolymer and derivatives, polyacrylic and methacrylic acid derivatives, carboxyvinylpolymers, cellulose derivatives: methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose and its salts.

These bioadhesive properties of said polymers may be determined by the methods disclosed in S.T.P. Pharma 4 (8) 688-697, 1988.

The adhesive and bioadhesive properties of the formulations reported below were tested using a suitable apparatus described in a previous work (Maggi, L., Giunchedi, P., Conte, U., La Manna, A., Acta

Technol. Legis Medic., 3, 13, 1992). The procedure consists of two steps: sample and substrate conditioning for adhesion setting, and fracture strenght determination. The sample is fixed to the holder and wetted with a defined volume of hydration fluid (mucin 2 w% aqueous solution). The sample is let to hydrate for 5 minutes, then the holder is rised towards the probe (quartz load washer), till the contact between the two surfaces is established. At this point a preload of 0.15 kg/cm^2 is applied for 2 minutes in order to establish adhesion bindings. The measurement starts when the holder is lowered at a constant speed, and ends when the two substrates are completely detached. A negative peak is obtained, maximum value of which represents the adhesive strenght.

The biocompatible bioadhesive polymers may also be used for semisolid formulations such as ointments, gels and the like.

These compositions contains the active component in an amount from 0.5 to 50% w/w and the classical excipients for gels or hydrophilic or lipophilic ointments (such as cellulose derivatives, carboxyethylcellulose, carboxyvinylpolymers) or special polymers such poloxamer (polyoxyethylene polyoxypropylene copolymers) with molecular weight higher than 3000 (such as Pluronic F 108, F 127, F 98, F 88 ecc.) and poloxamines (copolymers oxypropylene-oxyethylene-ethylenediamin) (Tetronic) used as gelifying agents in amounts ranging from 10 to 60% and characterized by sensitivity to temperature changes.

Particularly, Pluronic F 127, used in solution in

a suitable amount, has a low viscosity at room temperature whereas remarkably increases its viscosity at temperatures of 35-37°C. This causes a more stiff structure of the gelified medium and, as a consequence, the drug is released during a longer period of time.

For the preparation of tablets or other pharmaceutical forms for vaginal administration, excipients and technological additives suited to confer to the compositions the desired flowability and compactation characteristics as well as components useful to make the composition aesthetically acceptable, may also be used.

In order to evaluate the therapeutic characteristics of the compositions of the invention, clinical trials were carried out on vaginal effervescent tablets or slow-release bi-layered vaginal tablets containing 400 mg of acyclovir.

The results of the tests, carried out on 40 patients affected by relapsing Type 2 genital herpes treated with one tablet per day of Examples 1, 3 or 4, have shown that the compositions of the invention are able to induce the regression of symptomatology more rapidly and with a better tolerability in comparison with the conventional vaginal formulations.

The invention is further illustrated by the following Examples.

EXAMPLE 1

Effervescent tablets containing acyclovir

Unitary composition:

acyclovir	400.0 mg
lactose	900.0 mg
maize starch	242.0 mg
adipic acid	140.0 mg
sodium bicarbonate	110.0 mg
magnesium stearate	20.0 mg
stearic acid	8.0 mg
colloidal silica	8.0 mg
polysorbate 80	2.0 mg

Preparation

A granulate containing the active principle is prepared by mixing acyclovir and maize starch together with an aqueous solution of starch paste and polysorbate 80.

The wet mass is forced through a screen (710 µ). The granulate is then dried to constant weight and sieved again.

Colloidal silica is added thereto and the mixtur is mixed in a solid mixer for 10 minutes. Separately, a granulate containing adipic acid is prepared from lactose and maize starch. The two granulates are then mixed together in a powder mixer for 15 minutes. Sodium bicarbonate is then added and mixed for further 15 minutes. Stearic acid, magnesium stearate and colloidal silica (previously sieved) are finally added and mix d for further 20 minutes.

Tablets having ogival or almond shape and containing 400 mg of active principle are prepared from the obtained mixture.

EXAMPLE 2

Sustained-release bioadhesive acyclovir vaginal formulation

Unitary composition

acyclovir	200 mg
hydroxypropylmethylcellulose (Methocel K 4 M)	200 mg
mannitol	400 mg
maize starch	400 mg
adipic acid	70 mg
talc	20 mg
magnesium stearate	10 mg

The active component, hydroxypropylmethylcellulose, mannitol, maize starch and adipic acid, previously sieved on a 250 μ screen, are mixed for 20 minutes in a suitable powder mixer. The mixture is then added with magnesium stearate and talc and mixed for further 20 minutes.

Ogival tablets containing 200 mg of acyclovir are prepared from this mixture.

EXAMPLE 3

Sustained-release bioadhesive acyclovir vaginal formulation

Unitary composition

acyclovir sodium salt equivalent to acyclovir	400 mg
hydroxypropylmethylcellulose (Methocel K 4 M)	200 mg
mannitol	300 mg
maize starch	300 mg
adipic acid	70 mg
talc	20 mg
magnesium stearate	10 mg

Ogival tablets containing 400 mg of acyclovir are prepared by essentially the same method of Example 2.

EXAMPLE 4

Bi-layered vaginal tablets containing acyclovir

A first layer, effervescent, has the following unitary composition:

acyclovir	200.0 mg
lactose	500.0 mg
maize starch	122.0 mg
adipic acid	70.0 mg
sodium bicarbonate	55.0 mg
magnesium stearate	10.0 mg
stearic acid	4.0 mg
colloidal silica	4.0 mg
polysorbate 80	1.0 mg

The granulate is prepared according to the method of Example 1.

The second layer has the following unitary composition.

acyclovir	200 mg
hydroxypropylmethylcellulose (Methocel K 4 M)	200 mg
mannitol	400 mg
maize starch	200 mg
adipic acid	70 mg
talc	20 mg
magnesium stearate	10 mg

The active principle, hydroxypropylmethylcellulose, mannitol, maize starch and adipic acid, previously sieved, are mixed for 20 minutes in a suitable mixer. The mixture is then added with magnesium stearate and talc and mixed for further 20 minutes.

Bi-layered tablets are prepared using a suitable tabletting machine (Kilian or Manesty) equipped with ogival punches and matrices.

The bi-layered tablet, automatically obtained, contains 200 mg of acyclovir in the first effervescent layer and 200 mg of acyclovir in the second layer consisting of hydrophilic, gelifiable and bioadhesive matrix, from which the active component is released in about 24 hours.

The dosage forms prepared with the formulations described in example 2, 3 and 4, show good adhesion properties. The adhesion forces, measurd with th

apparatus previousely described, range from 0.27 to 0.50 kg/cm^2.

CLAIMS

1. Biocompatible sustained-release vaginal compositions containing antiviral drugs.

2. Compositions according to claim 1, wherein the antiviral drug is selected from: acycloguanosine (acyclovir) or its salts or derivatives, trifluridine, bromovinyldeoxyuridine, desciclovir, enviroxime, foscarnet sodium, ganciclovir, idoxuridine, inosine pranobex, interferons (α, β, γ), rimantadine hydrochloride, ribavirine, vidarabine and derivatives, zidovudine or azidothymidine.

3. Compositions according to claim 2, wherein the antiviral drug is acyclovir its salts and derivatives.

4. Compositions according to any one of the previous claims in form of hydrophilic tablets, slowly erodible and/or disgregable.

5. Compositions according to claim 1, 2 or 3 in form of bioadhesive hydrophilic tablets.

6. Compositions according to claim 1, 2 or 3 in form of bi-layered tablets, wherein a first layer is able to release immediately the drug and the second layer provides the sustained release of the drug by means of bioadhesive polymers.

7. Compositions according to claim 1, 2 or 3 in form of effervescent tablets.

8. Compositions according to claim 1, 2 or 3 in form of vaginal washes containing bioadhesive polymers.

9. Compositions according to claims 5, 6 or 8 containing biocompatible bioadhesive polymers selected from gelatine, xantanes, scleroglucane, collagene,

pectine and amylopectine, dextranes, hyaluronic or polygalactouronic acid, alginic acid, alginates, polyvinylpyrrolidone, polyvinylalcohol, polyethylenglycols, polypropylenglycols and copolymers, polymethylvinylether maleic anhydride copolymer and derivatives, polyacrylic and methacrylic acid derivatives, carboxyvinylpolymers, cellulose derivatives, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose and its salts.

10. Compositions according to claim 1, 2 or 3 containing a polymer or a mixture of polymers biocompatible and/or bioadhesive in amounts varying from 5 to 95 w/w%, but preferably from 15 to 60% with respect to the dosage from weight.

11. Compositions according to claim 1, 2 or 3 containing a biocompatible and/or bioadhesive polymer a mixture of polymers with the same average molecular weight but different substitution characteristics and/or degree of substitution (namely different hydrophilic properties and/or gelation or erosion rates).

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/01655

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/00; A61K9/20; A61K31/52

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0 255 902 (TOFCO SA) 17 February 1988 see column 4 - column 5; examples 1-5 see claims	1,4,9
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Y	EP,A,0 020 777 (TEIJIN LIMITED) 7 January 1981 see page 8, line 4 - line 28 see page 15 - page 16; example 4	6-8,11 6,11

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IV. CERTIFICATION

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EUROPEAN PATENT OFFICE	BOULOIS D.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

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Y	FR,A,2 355 510 (TOKO YAKUHIN KOGYO KABUSHIKI KAISHA) 20 January 1978 see page 2, line 5 - line 30 see page 6, line 1 - line 15 see page 14; example 22	8
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Y	US,B,4 389 393 (SCHOR J.M. ET AL) 22 October 1985 see column 8 - column 9; example 5	11

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

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X	US,A,4 983 393 (COHEN R.S. ET AL) 8 January 1991 see column 3, line 51 - line 61 see column 4, line 51 - column 5, line 12 see column 8; example 9 see claims 1,4	1,4

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9201655 SA 63088

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